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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,171	04/29/2009	**Laura M'Rabet**	207,645	2577

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,171	M'RABET ET AL.	
	Examiner	Art Unit	
	MAGDALENE SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *28-50* is/are pending in the application.

5a) Of the above claim(s) *35-47* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *28-34 and 48-50* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/15/2006*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence non-compliant*

DETAILED ACTION

Claims **28-50** are pending. Claims **1-27** are canceled. The amendment to the claims dated 11/15/2011 has been acknowledged.

Applicant's election without traverse of group I in the reply filed on 11/15/2011 is acknowledged.

Claims **35-47** are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/15/2011.

Claims **28-34, 48-50** are under consideration.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37CFR 1.821(a)(1) and (a)(2). For example, on pages 19-20, Table 1 of the specification nucleotide sequences for primers are disclosed but are not identified by sequence identification numbers and have not been included in Applicant's sequence listing received on 04/29/2009. As such, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached **N**otice To Comply With Requirements For Patent Applications Containing **N**ucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. *Any* response to this Office Action, which fails to meet all of these requirements, will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Claim Objections

Claims **28-34, 48-50** are objected to because each claim begins with "Method…" which lacks the article "A method" that is grammatically correct. MPEP § 608.01(m) states that, "Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations. See *Fressola v. Manbeck,* 36 USPQ2d 1211 (D.D.C. 1995)." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims **28-34, 48-50** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of lung airway hyper-responsiveness induced by non-specific inhaled irritants, in a mouse suffering from induced emphysema, comprising oral administration of a composition comprising an effective amount of between about 1×10^6 and about 1×10^{12} colony forming units of lactic acid producing bacterium (LAB) strain LMG-22110, which has a beneficial effect on airway hyper-responsiveness determined by measuring the enhanced pause value (PenH) of a test mouse, does not reasonably provide enablement for: a) treating or prophylaxis of any lung related dysfunctions encompassed by the full scope of the claims in any subject including human, and b) wherein any LAB is administered via any route of administration or any amount of LAB colony forming units. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The invention is directed to method for the treatment or prophylaxis of lung dysfunction selected from the group consisting of Chronic Obstructive Pulmonary Disease (COPD), aspiration, lung dysfunction due to non-specific inhaled irritants, pulmonary oedema, and tracheal stenosis in a subject, comprising administration of a composition comprising lactic acid producing bacterium (LAB) which has a significant beneficial effect on airway narrowing determined by measuring the enhanced pause value (PenH) of a test animal. Further embodiments recite that the method according to claim 28, wherein said composition further comprises one or more carriers and/or proteins, and/or carbohydrates, and/or lipids and/or anti-oxidants, and is in liquid, powder, solid or capsulated form.

Breadth of the claims. The claims broadly encompass treating or prophylaxis lung dysfunction any of the numerous lung disorders in any subject by administering any amount of LAB.

Guidance of the Specification/The Existence of Working Examples. The specification teaches BALB/c mice were sensitized by intraperitoneal (i.p) injections with ovalbumin on days 0 and 7 and challenged on days 35, 38, and 41 by inhalation of ovalbumin aerosols, and the mice were treated daily with 10^9 colony forming units (CFU) lactic acid bacteria strain LMGvP-2210 orally via gavage starting at day 28 thru day 42. The airway responsiveness was

determined as enhanced pause (PenH). After measurement of cholinergic airway responses by PenH, animals were sacrificed and bronchoalveolar lavage was performed, total number of cells was determined (neutrophils, macrophages, eosinophils+lymphocytes) as a measure of lung tissue inflammation. LMG P-22110 resulted in a decreased number of lung inflammation of neutrophils, macrophages, osinophils+lymphocytes (example 2 and Table 3 on p 24).

The specification also teaches lung emphysema was induced by intranasal administration of LPS in mice treated with 10^9 colony forming units (CFU) lactic acid bacteria strain LMG P-2210 orally via gavage starting at day 14 thru day 42 and airway responsiveness and bronchoalveolar lavage were determined as described in Example 2. In addition hypertrophy of the right ventricular in the heart is an indication for lung emphysema. The whole heart was isolated and the right ventricular hypertrophy was assessed. LMG P-22110 resulted in a significant effect on airway hyper-responsiveness and right ventricular hypertrophy (example 3 and Table 4 on p 26).

State of the Art/Predictability of the Art. It is noted that the working example 2 in the specification is directed to ovalbumin sensitized and ovalbumin challenged mice orally treated with strain LMG P-22110 LAB resulted in decreased lung inflammation for prophylaxis said lung dysfunctions. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that the recitation encompasses the prophylaxis of said lung dysfunctions in any subject, which are not known to have as single recognized cause. Applicants' claims embrace prophylaxis of a lung dysfunction selected from the group consisting of Chronic Obstructive Pulmonary Disease (COPD), aspiration, lung dysfunction due to non-specific inhaled irritants, pulmonary oedema, and tracheal stenosis in a subject, comprising administering LAB. However, the specification fails to provide guidance with regard to prophylaxis of said lung dysfunctions via art recognized procedural and methodological steps.

Lung dysfunctions develop because of inherited and environmental contribution factors. In addition the prophylaxis of lung dysfunctions such as Chronic Obstructive Pulmonary Disease (COPD), aspiration, lung dysfunction due to non-specific inhaled irritants, pulmonary oedema, and tracheal stenosis have several causes which include food, environmental irritants, cigarette smoking, secondhand smoke, air pollution and occupational exposure to irritants with cigarette smoking to mention a few. Moreover, said lung related dysfunctions are known to be involved various, many possible, different, separate and independent, even unknown pathology, etiologies or symptoms. The specification has not provided guidance to correlate a decrease in the number of inflammatory cell of the ovalbumin sensitized and challenged mice resulted in the decreased lung inflammation as to how said lung dysfunctions can be prevented or prophylaxis, since there are numerous contribution factors that promote said lung dysfunctions and also since prophylaxis of having the disease means that it is uncertain that the disease would eventually definitely occur in the first place. Regarding claim 33, embracing a broad spectrum of carriers, the skilled artisan would view that treating or prophylaxis of any lung dysfunction by administering any said carriers as being highly unpredictable. The specification has not provided guidance of the broad treatment or prophylaxis of any lung dysfunctions recited in the instant claims suitable to practice the claimed invention.

For example, **Villena et al** (Int Immunopharmacology, 11(11):1633-45, 2011) teaches that it is needed further studies using immunomodulatory LAB strains able to stimulate respiratory immunity as well as their cell components such as nonviable bacterial particles, intact cell walls, cell wall polysaccharidepe ptidoglycan complex and chromosomal DNA are necessary to find probiotic effector molecules able to stimulate immunity in distant mucosal sites from the gut (1643, 1st column, 1st paragraph). Villena teaches the immunostimulating properties of LAB have been proved to be strain- and dose-dependent and consequently, the

ability of LAB to increase resistance against pneumococcal infection was studied using several *Lactobacillus* and *Lactococcus* strains and different doses and periods of administration and only four of the treatments assayed increased the resistance of the mice to challenge with the respiratory pathogen: administration of *Lactobacillus casei* CRL431, a probiotic strain with widely documented immunomodulatory properties, *Lactococcus lactis* NZ9000, a strain used for the expression of heterologous proteins, *Lactobacillus rhamnosus* CRL1505, a new probiotic strain isolated from goat milk with optimum technological properties, and a probiotic yogurt prepared with the immunobiotic strains *Lactobacillus bulgaricus* CRL423 and *Streptococcus thermophilus* CRL412 (p 1634, 2nd column, 2nd paragraph). **Wells et al** (Nature Reviews Microbiology, 6: 349-362, 2008) teaches using the same mouse strain as a recipient, strains of *L. lactis* and *Lactobacillus* spp. that produce tetanus toxin fragment C (TTFC) have been shown to independently elicit protective immune responses to challenge with tetanus toxin, but these studies cannot be directly compared because of differences in dosage and other methodologies (p 353, 1st column, 3rd paragraph) because the best location of an expressed antigen for optimal mucosal immunization cannot yet be conclusively identified (p 353, 2nd column end of last paragraph). Wells teaches killed LAB safety of intranasal immunization needs to be validated and based on the protection studies that have been performed in small animals, it is difficult to predict whether the necessary dose for humans will be feasible and vaccination studies in larger animals should help clarify these issues (p 360, 2nd column 1st paragraph).

Thus, the skilled artisan would the skilled artisan would view that the prophylaxis of said diseases which are characterized as having many contribution factors and causes in any subject by administering any LAB via any route of administration at any amount of LAB to a subject as being highly unpredictable.

An artisan would not know how to use or make the instant invention in a predictable ad reproducible fashion from the teachings of the instant specification or the art. The breadth of the claims encompasses any strain of LAB, any mode of administration in any effective amount of LAB in any subject. The specification fails to provide any specific guidance with regard to sine there are numerous contribution factors that promote said lung dysfunctions and also since prophylaxis of having the disease means that it is uncertain that the disease would eventually definitely occur in the first place, and since LAB strains able to stimulate respiratory immunity as well as their cell components such as nonviable bacterial particles, intact cell walls, cell wall polysaccharide peptidoglycan complex and chromosomal DNA are necessary to find probiotic effector molecules able to stimulate immunity in distant mucosal sites from the gut as taught in the art and in the instant case mucosal cells of the lung.

The Amount of Experimentation Necessary. Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for treating or prophylaxis any lung dysfunction disease any mode of LAB administration any LAB strain and any LAB dose of a disease, the lack of direction or guidance provided by the specification for treating or prophylaxis any lung dysfunction disease any mode of LAB administration any LAB strain and any LAB dose, the absence of working examples that correlate to the treatment or prophylaxis any lung dysfunction disease any mode of LAB administration any LAB strain and any LAB dose, the undeveloped state of the art pertaining to treating or prophylaxis any lung dysfunction disease any mode of LAB administration any LAB strain and any LAB dose, and the breadth of the claims directed to all lung dysfunction diseases and LAB strains, doses and modes of administration, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **28, 30-31, 34, 48-50** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Clancy** (WO 01/37865 A1; published 31 May 2001 (IDS)) in view of **Hamelmann et al** (Am J of Respiratory and Critical Care Medicine, 156(3): 766-775, 1997 (IDS)).

Regarding claims **28, 30-31**, Clancy teaches the use of oral probiotics such as Lactobacillus acidophilus and/or Lactobacillus casei and having the capacity to down regulate IgE antibody, and thus preventing and/or treating allergic disease and its use in asthma , wherein C57/B16 mice were fed 10^{10} Lactobacillus before or 24 hours after sensitization with ovalbumin (OVA) resulting in suppression of IgE response to OVA by Lactobacillus after allergen sensitization (example 2, p 9and figure 3) and in example 3 Example 3 Clancy teaches suppression of IgE response to OVA by Lactobacillus is dose-dependent (p 9). Clancy also teaches in example 3 mice were fed orally with 10^{8}, 10^{9} or 10^{10} Lactobacillus before they were sensitized 24 hours later with OVA (p 9).

Regarding claims **34, 48-50**, Clancy teaches mice were fed orally with 10^{8}, 10^{9} or 10^{10} Lactobacillus (p9 and p 11 claims 10-11).

Clancy does not specifically teach to have a significant beneficial effect on airway narrowing determined by measuring the PenH.

However, at the time of filing, **Hamelmann** teaches the use of Brometric whole -body plethysmography and increases in enhanced pause (PenH) as an index of airway obstruction in order to measure in vivo airway responsiveness in allergic mice, thus airway hyperesponsiveness as a major symptom of bronchial asthma is able to be measured by a noninvasive method (under discussion p 773-774).

Accordingly, it would have been obvious to the skilled artisan to modify the teachings of Clancy, to use Brometric whole -body plethysmography for measuring the enhanced pause (PenH) as an index of airway obstruction in order to measure in vivo airway responsiveness in allergic mice as taught by Hamelmann with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification in order to measure airway hyperesponsiveness as a major symptom of bronchial asthma by Pen H a noninvasive method and particularly in view of the teachings of Clancy that oral probiotics such as Lactobacillus acidophilus and/or Lactobacillus casei and having the capacity to down regulate IgE antibody, and thus preventing and/or treating allergic disease and its use in asthma and suppression of IgE response to OVA by Lactobacillus is dose-dependent (p 9). .

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claims **28, 29** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Clancy** (WO 01/37865 A1; published 31 May 2001 (IDS)) in view of **Hamelmann et al** (Am J of Respiratory and Critical Care Medicine, 156(3): 766-775, 1997 (IDS)) and further in view of **Guarino (**Abstract, Gastroenterology, 116(4(2): pA885, 1999).

The teachings of Clancy /Hamelmann apply here as indicated above.

Clancy /Hamelmann do not specifically teach further comprising at least one bacterium having anti-inflammatory activity for treating cystic fibrosis.

However, at the time of filing, Guarino teaches the use of LAB for oral probiotics such as Lactobacillus casei GG (LGG) in cystic fibrosis where an improvement of lung function results in reduction in the incidence and duration of exacerbations as well as rise of forced espiratory volume, wherein LGG counteracts stimulation of immune response (thus anti-inflammatory property) (abstract).

Accordingly, it would have been obvious to the skilled artisan to modify the teachings of Clancy /Hamelmann, to use Lactobacillus casei GG (LGG) having anti-inflammatory activity as taught by Guarino with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification in order to improve lung function in cystic fibrosis because a method of enhancing treatment of cystic fibrosis was made part of the ordinary capabilities of one skilled in the art based upon the teachings of Guarino. One of ordinary skill in the art would have been capable of applying this known Lactobacillus casei GG (LGG) and the results would have been predictable to one of ordinary skill in the art.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAGDALENE SGAGIAS whose telephone number is (571)272-3305. The examiner can normally be reached on Monday-Friday, 9-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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